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A Review of the Food and Drug Administration Adverse Event Reporting System for Tramadol-Related Hypoglycemia

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A Review of the Food and Drug Administration Adverse Event Reporting System for Tramadol-Related Hypoglycemia

Abstract

Background: Hypoglycemia is a rare adverse effect of tramadol that is described in the medical literature and package insert. **Objective:** The purpose of this study was to review reports of tramadol and hypoglycemia in the Food and Drug Administration Adverse Event Reporting System (FAERS) database to determine a potential association. **Methods:** Disproportionality analysis with Bayesian correction was used to compare tramadol and hypoglycemia with other medications in FAERS. The results were considered significant if the fifth percentile of the Empirical Bayesian geometric mean distribution (EB05) >2. Logistic regression odds ratios was used to determine if age, diabetes medications, and renal insufficiency masked the disproportionality of hypoglycemia, with the fifth percentile of the logistic regression odds ratio (LR05) >2 indicating a potential signal. The Interaction Signal Score (INTSS) was computed to determine the influence of predisposing risk factors on the signal. **Results:** A total of 605 cases of tramadol-associated hypoglycemia were reported, but our results were not significant (EB05: 1.590). Tramadol-associated hypoglycemia was significant in patients who did not take diabetes medications (EB05: 2.256; LR05: 2.2104). Renal insufficiency was not found to increase the risk of tramadol-associated hypoglycemia (INTSS: 0.865). There was a significant signal for tramadol-associated hypoglycemia in patients aged 0 to 1 year (LR05: 3.0240) and 2 to 4 years (LR05: 2.6853). **Conclusion and Relevance:** Results of our analysis suggest a potential signal between hypoglycemia and tramadol use in patients not taking diabetes medications. Our results do not support a predisposition for tramadol-associated hypoglycemia in patients with renal insufficiency, increasing age, and/or diabetes as noted in the tramadol package insert.

Disciplines

Pharmacy and Pharmaceutical Sciences

Comments

Abstract:

Background: Hypoglycemia is a rare adverse effect (AE) of the central analgesic tramadol that is described in the medical literature and package insert.

Objective: The purpose of this study was to review reports of tramadol and hypoglycemia in the Food and Drug Administration Adverse Event Reporting System (FAERS) database to determine a potential association.

Methods: Disproportionality analysis with Bayesian correction was used to compare tramadol and hypoglycemia with other medications in FAERS using Empirica Signal Software. The results were considered significant if the fifth percentile of the Empirical Bayesian geometric mean (EBGM) distribution (EB05) > 2. Logistic regression odd-ratios (LROR) was used to determine if age, diabetes medications, and renal insufficiency masked the disproportionality of hypoglycemia with LR05 > 2 indicating a potential signal. The Interaction Signal Score (INTSS) was computed to determine the influence of predisposing risk factors' on the signal.

Results: Six hundred and five cases of tramadol associated hypoglycemia were reported in the FAERS database, but our results were not significant (EB05: 1.590). Tramadol associated hypoglycemia was significant in patients who did not take diabetes medications (EB05: 2.256; LR05: 2.2104). Renal insufficiency was not found to increase the risk of tramadol associated hypoglycemia (INTSS: 0.865). There was a significant signal for tramadol associated hypoglycemia in patients aged 0-1 years (LR05: 3.0240) and 2-4 years (LR05: 2.6853).

Conclusion and Relevance: Results of our analysis suggest a potential signal between hypoglycemia and tramadol use in patients not taking diabetes medications. Our results do not

support a predisposition for tramadol associated hypoglycemia in patients with renal

insufficiency, increasing age, and/or diabetes as noted in the tramadol package insert.

Introduction:

Tramadol is a central analgesic that is commonly used for the treatment of moderate to severe, acute and chronic pain. Tramadol has a low binding affinity for μ opioid receptors. Its antinocceptive effects are primarily related to its active metabolite O-desmethyltramadol (M1) which has a higher affinity for μ opioid receptors than tramadol and inhibition of neuronal re-uptake of norepinephrine and serotonin.[1] It is metabolized in the liver and the formation of its active metabolite M1 is dependent on CYP2D6. In vivo studies suggest tramadol centrally modulates glucose levels through μ opioid receptor agonism and increased levels of serotonin.[2,3]Tramadol had the highest number of reported opioid associated hypoglycemia cases among 9 opioids studied in a recent disproportionality analysis using the World Health Organization's (WHO) pharmacovigilance data VigiBase® suggesting that hypoglycemia might be more unique to tramadol compared to other analgesics with effects on the μ opioid receptor.[4]

Tramadol associated hypoglycemia has been increasingly described in the medical literature since 2006.[5] Hypoglycemia is reported as a rare side effect listed in the package insert.[1] It is suggested that low glucose levels are more likely to occur in patients with predisposing risk factors such as renal insufficiency, diabetes, and increasing age. Twelve reports have been published about tramadol induced hypoglycemia in English between 2009-2018 representing the United Kingdom, United States of America, Australia, India, Saudi Arabia, Qatar, Iran, France, Nigeria, Italy and Taiwan.[6-17] Spontaneous, voluntary reporting systems such as the United States FAERS database serve as a valuable resource for identifying rare side effects that are less likely to emerge during costly, time-limited clinical trials enrolling homogeneous patient populations of limited size. A limitation of FAERS and similar databases is the lack of reliable exposure information as well as a control group, but this can be partially overcome through the

3

use of disproportionality analysis. Disproportionality analysis compares the occurrence of an AE of interest with a specific drug to the occurrence of the same AE with comparable medications or all other Food and Drug Administration (FDA) approved medications through the use of an adverse event relative reporting ratio (RR).[18] Furthermore disproportionality scores utilizing a Bayesian approach are less likely to be influenced by chance when identifying potential correlations, or signals for rare events. The purpose of this study was to review reports of tramadol and hypoglycemia in the FAERS database to determine a potential association.

Methods:

This study is a qualitative and quantitative review of cases in the FAERS database between November 1968 and December 31, 2018 (fourth quarter of 2018).   Reported cases of tramadol and hypoglycemia were compared to all reported commercially available non-biologic medications in FAERS using the Empirica Signal Software version 8.1.1.1 (Oracle Health Sciences, Redwood Shores, CA). Medical dictionary for regulatory activities (MedDRA) codes for "hypoglycaemia" (MedDRA Code 10020993) and "renal impairment" (MedDRA Code 10062237) were used to identify cases in the FAERs database. Since cases in FAERs are based on the reporter's assessment, use of MedDRA codes can overcome individual inconsistencies in terminology by grouping similar terms that relate to the same condition or AE of interest. We analyzed from the start of adverse event data collection by the FDA in 1968 (substance registration system , AERS and FAERS databases) to provide more comprehensive comparator data even though tramadol was not FDA approved until March 3, 1995.[19]

Other medications in the FAERS database with μ opioid agonist effects including methadone, hydromorphone, codeine, morphine, oxycodone, hydrocodone, fentanyl, buprenorphine, and tapentadol were also evaluated as background comparators.

Disproportionality analysis was conducted for tramadol and each opioid using an empirical

Bayesian approach based on the relative report ratio (RR) which is defined as:[18]

RR = N/E

N= number of case reports for a drug and hypoglycemia

E = number of expected hypoglycemia events if there was no relationship between the drug

exposure and hypoglycemia

We assume for E that medication exposure and hypoglycemia are independent. Therefore E is

calculated:

E = (percent of cases in the FAERS database with drug) X (percent of cases in the FAERS

database with hypoglycemia) X (total number of cases in the FAERS database)

Empirical Bayesian geometric mean (EBGM) is a Bayesian correction of the RR based on prior

distribution of all reporting ratio values in the database.[20] To be consistent with earlier FDA

publications[21], the results of the disproportionality analysis were considered significant if the

fifth percentile of the EBGM distribution was greater than or equal to 2 (EB05 of > 2).[22]

Logistic regression was used to control for covariates and determine if predisposing risk factors

cited in the package insert, age, concomitant use of diabetes medications, and renal insufficiency,

were associated with tramadol induced hypoglycemia.[23] Logistic regression odd-ratios (LROR)

were used with a LR05 > 2 indicating significance, similar to an EB05. The Interaction Signal

Score (INTSS) was computed where appropriate to determine if the impact of predisposing risk

factors influenced the signal or lack thereof.[24]

Results:

Six hundred and five cases of tramadol associated hypoglycemia were reported between November 1968 and December 31, 2018 in the FAERS database. There is not sufficient information provided in the FAERS database to perform a complete causality assessment for each individual case. The number of cases has consistently increased over time (figure 1) and tramadol has the strongest association with hypoglycemia among the medications with μ opioid agonist properties that we studied (figure 2). Despite an increasing number of cases over time and an elevated EB05 the level did not reach statistical significance (EB05: 1.590). The FAERS database contains fields for medication dechallenge and rechallenge information, but these are only sparsely populated. Out of 605 case reports of tramadol and hypoglycemia, only 12 contain both dechallenge and rechallenge information, 141 contain only dechallenge information and no rechallenge information, and 18 contain only rechallenge information and no dechallenge information. The numbers above are relatively small compared to the total number of cases involved, therefore the significance of dechallenge and rechallenge information with respect to the overall results may be limited. Codes for tramadol's reported role in the adverse event was provided in the FAERS database (table 1). Multiple references to tramadol in the same case may be characterized by multiple role codes, which accounts for the total number of role codes exceeding the number of cases. Cases of tramadol associated hypoglycemia in patients taking and not taking diabetes medications were separated and further analyzed using logistic regression. There were 352 cases of tramadol associated hypoglycemia in patients taking concurrent diabetes medications (58%) and 253 cases among tramadol users who did not take antidiabetic agents (42%).   Tramadol associated hypoglycemia resulted in a significant signal in patients not taking diabetic medications (EB05: 2.256; LR05: 2.2104), but a signal was not detected in patients receiving concomitant antidiabetic agents (EB05: 0.856; LR05: 1.5631). Ten

cases of tramadol related hypoglycemia were found in patients with renal impairment but this result was not significant (EB05: 1.572). An INTSS of 0.865 confirmed that renal function is unlikely to influence the occurrence of hypoglycemia. Age as a variable alone was not found to increase the odds for tramadol associated hypoglycemia (LR05: 1.6425). However, additional analysis of age group covariates indicated younger patients, ages 0-1 years (LR05: 3.0240) and 2-4 years (LR05: 2.6853) (table 2) are more likely to experience tramadol related hypoglycemia.

Discussion:

Based on our results tramadol is the most likely analgesic analyzed with opioid activity to be associated with hypoglycemia. The exact mechanism of hypoglycemia is not well defined, but several hypotheses exist. Cheng et al. observed that tramadol administration decreased plasma glucose in rats with streptozotocin (STZ) induced diabetes and that were mitigated by the administration of naloxone.[2] Investigators proposed μ opioid receptor activation stimulates glucose uptake in the periphery via increased glucose transporter subtype 4 (GLUT4) gene expression in skeletal muscle. They also postulated tramadol decreased phosphoenolpyruvate carboxykinase (PEPCK) enzyme expression in the liver slowing gluconeogenesis leading to reduce blood glucose levels Interestingly a change in blood glucose was not observed after fluoxetine administration and p-chlorophenylalanine (PCPA) injection to increase and decrease respectively endogenous serotonin (5-HT). The authors concluded the tramadol associated hypoglycemia is not related to tramadol's effects on serotonin, rather μ opioid receptor agonism in the periphery. Norepinephrine administration in controlled settings have shown to increase glucose concentrations and has not been implicated as a potential mechanism for tramadol's hypoglycemic activity.[25] Choi et al. also found an association between tramadol administration and decreased blood glucose in rats with 90% pancreatectomy to induce diabetes.[3] It was

hypothesized that μ opioid receptor activation increased glucose utilization centrally through potentiation of the insulin-signaling cascade in the cerebral cortex and hypothalamus through induction of insulin receptor substrate 2 (IRS2) expression. Naloxone again reversed hypoglycemic effects of tramadol similar to Cheng's findings supporting the role of the μ opioid receptor in tramadol associated hypoglycemia. The Cheng and Choi studies only investigated tramadol associated hypoglycemia in diabetic rats. It is unclear if the findings of Cheng and Choi would demonstrate greater potential for glucose lowering effects with tramadol if the studies were repeated in non-diabetic mice.

Serotonin is known to decrease blood glucose in rats despite the lack of an affect noted previously.[26,27] A study performed by Chi et al. assessed the impact of direct serotonin administration on blood glucose in rats with and without STZ induced diabetes. The authors found a positive association between lowering of blood glucose in both non-diabetic and diabetic rates in addition to increased serum levels of β-endorphin. Interestingly naloxone blunted the glucose lowering effects while serotonergic antagonists not only abolished this effect but also limited β-endorphin release. This illustrates how both the opioid and serotonergic properties of tramadol may contribute to the reports of hypoglycemia seen in our study.

Hypoglycemia is a rare AE of analgesics with μ opioid receptor agonist properties. The most comprehensive data to date includes analysis of opioid associated hypoglycemia using the WHO's VigiBase® pharmacovigilance database for signal detection and the French PharmacoVigilance Database (FPVDB) for validation using descriptive statistics.[4] There were 100,472 reports of opioid associated hypoglycemia and 28,113 cases of tramadol related hypoglycemia in VigiBase® between 1967-April 1, 2018. Results of their analysis in VigiBase® indicated an adjusted reporting odds ratio (aROR): 1.53 (95% CI: 1.52-1.54) for opioid

associated hypoglycemia and an aROR: 1.28 (95% CI: 1.26-1.30) for tramadol associated

hypoglycemia. An aROR of > 1 is considered significant. One hundred-thirty-three cases of

opioid associated hypoglycemia and 93 cases of tramadol associated hypoglycemia were

recorded in the FPVDB.   In both databases, tramadol was the most likely opioid to contribute to

the occurence of hypoglycemia. We found methadone to the have the second highest EB05 for

hypoglycemia among the medications with μ opioid agonist effects that we studied, although the

results did not support a strong signal (EB05: 1.422). Interestingly of the nine opioids analyzed

in VigiBase(R) tramadol was not associated with the strongest signal for hypoglycemia, rather,

hydromorphone was (aROR 1.97) and tramadol (aROR 1.28) had the second lowest signal

detection only succeeding codeine (aROR 1.09). Methadone was the second largest signal

detection with an aROR 1.92. Tramadol and methadone both have effects on serotonin in

addition to their μ opioid agonist properties.[1,28] Their potential hypoglycemia effects may be

partially related to stimulation of the 5-HT7 receptor on adrenal gland as described by Chi et al.

in addition to the mechanisms proposed by Choi et al. and Cheng et al.[2,3,27]

Quantitative signal detection in itself is not sufficient to support a causal relationship, but it may

be used to strengthen a hypothesis originally developed through clinical observations and

literature evaluation. It can elevate the hypothesis from an effect observed in isolated case

reports or a limited number of clinical studies to a statistical relationship observed in complete

populations or detect specific subpopulations with predisposing factors associated with a single

adverse reaction or a complex of related symptoms. The results of our study suggest that the

three subpopulations noted to have a predisposition for tramadol associated hypoglycemia in the

package insert, patients with renal insufficiency, increasing age, and/or diabetes did not have an

increased risk. We identified a stronger signal for tramadol associated hypoglycemia in patients

not taking diabetes medications (EB05: 2.256) versus those using antidiabetic agents (EB05: 0.856). This result may be related to masking/cloaking which is suspected when the medication studied causes the AE of interest but other medications more commonly induce the same AE in the background, producing an artificially decreased disproportionality score.[29,30] Reports exist in the FAERS database of hypoglycemia associated with tramadol, diabetes medications, and combinations of both. Tramadol was not found to have a significant signal (EB05: 1.590) when all 605 reports of hypoglycemia with tramadol were assessed in the FAERS database. Using the WHO anatomical therapeutic chemical (ATC) classification, we were able to separate the cases of tramadol associated hypoglycemia in patients taking diabetes medications (ATC code A10, n=352) from those of patients not taking antidiabetic drugs (n=253). Further analysis illustrates that the signal for hypoglycemia in the database is likely masked due to the use of diabetic medications. In isolation a positive signal for disproportionality was only detected in patients not reported to be on diabetic medications. Individual cases of hypoglycemia observed with tramadol might have been associated with the fact that a number of these patients were diabetics, and therefore a likely alternative explanation for the occurrence of hypoglycemia would be available in these cases. It was possible to identify the impact of the presence of a diabetic subpopulation on the overall body of tramadol-related hypoglycemia observations with quantitative signal detection techniques. When the use of diabetic medications was controlled for utilizing logistic regression, an association was again found only for patients not taking concomitant medications for diabetes. A significant result for both the EB05 and LR05 in patients not taking diabetic medication illustrate that the signal strength for disproportionality for tramadol and hypoglycemia is reduced by the use of medications for diabetes. Future studies should explore the impact on specific diabetic medication classes and the occurrence of tramadol induced

hypoglycemia. Renal impairment was not found to have a significant signal for tramadol related

hypoglycemia (EB05: 1.572) among the 10 reported cases and was confirmed by an INTSS of

<1. Age also did not increase the risk of tramadol associated hypoglycemia (LR05: 1.6425),

except in patients between 0-1 years (LR05: 3.0240) and 2-4 years (LR05: 2.6853).

This study has several limitations that impair our ability to identify additional patient specific

factors that may be signals for tramadol associated hypoglycemia based on gaps in the clinical

literature and/or inconsistencies with FAERS database reporting. There is potential for

fluctuations in reporting patterns and underreporting of AEs and patient case data given that the

submission of cases to FAERS is voluntary. Although the use of the MedDRA standard

terminology overcomes some reporting inconsistencies, hypoglycemia can be defined in

different ways in MedDRA, which may lead to different outcomes. There is conflicting evidence

in the literature to identify if dose or gender increase the potential for tramadol associated

hypoglycemia.[4,9,13,16,17] Golightly et al. observed that tramadol associated hypoglycemia was

more likely to occur in younger patients (mean age 52.0 years versus 59.8 years; p=0.027) and

not those with concurrent kidney disease.[13] These findings are consistent with our findings, but

do not support that patients with renal insufficiency and increasing age are predisposed to

develop tramadol associated hypoglycemia as listed in the tramadol package insert.[1] Golightly et

al. excluded patients < 18 years so it is unknown if they would have observed an increased risk

of tramadol related hypoglycemia in patients < 4 years.[13] Separate from our findings, tramadol

should already be avoided in pediatric patients due to the risk of respiratory depression as listed

in the current package insert's black box warnings.[1] Recent initiation of tramadol is identified as

a risk factor but is not consistently reported within the FAERS database cases for further

analysis.[9,11] Other hypothesized risk factors such as variance in CYP2D6 metabolism or the

impact of underlying diabetes in patients not taking antidiabetic agents are not reported in the clinical literature or consistently within the FAERS patient cases.

There is significant heterogeneity in the types of literature reporting tramadol associated hypoglycemia especially with trial design, statistical tests, covariates, and study inclusion and exclusion criteria.[4,6-17] Two case-control studies of diabetic and non-diabetic patients by Golightly et al. and Fournier et al. support our findings that there is a stronger signal for tramadol associated hypoglycemia in patients not taking diabetes medications.[9,13] Golightly et al. reported an increased risk of hypoglycemia in tramadol patients who were not diabetic compared to oxycodone patients with hypoglycemia who were not diabetic [RR: 3.12 (95% CI: 1.53-6.51)]. There was a higher incidence of hypoglycemia with tramadol compared to oxycodone in type 1 and type 2 diabetics than non-diabetics, but the occurrence rate was only statistically significant in patients without diabetes ($p<0.001$). Fournier et al. noted an increased risk of hypoglycemia in tramadol users taking concurrent diabetes medications [adjusted OR: 2.12 (95% CI: 1.18-3.79)] compared to patients without diabetic medications [adjusted OR: 1.11 (95%CI: 0.76-1.64)] ($p=0.02$).[9] Pediatric patients were only included in the study by Nasouli et al. and case report by Aliyu et al.[10,14] The pediatric patients included in these publications experienced tramadol associated hypoglycemia after a tramadol overdose. Chretien et al. utilized the covariates of age, gender, and concurrent reporting of drugs used in diabetic patients in their multivariate logistic regression model to calculate aROR but did not report how each individual may have affected signal detection.[4] Direct comparisons between our study and Chretien et al. should be avoided due to differences in statistical methods.

Conclusion and Relevance:

We identified 605 cases of tramadol associated hypoglycemia in the FAERS database between November 1968 and December 31, 2018. There were 352 cases of tramadol associated hypoglycemia in patients taking concurrent diabetes medications (58%) and 253 cases among tramadol users who did not take antidiabetic agents (42%). Results of our analysis suggests a potential signal between hypoglycemia and tramadol use in patients not taking diabetes medications and patients < 4 years. Our results do not support a predisposition for tramadol associated hypoglycemia in patients with renal insufficiency, increasing age, and/or diabetes as noted in the tramadol package insert.

It is important to note that our findings do not indicate causality and require further epidemiological studies for confirmation in these subpopulations.

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Table 1: Tramadol Drug Role Code Assessment

Drug role code	N
Concomitant	339
Interacting	3
Other	2
Suspect	282
- Primary	177
- Secondary	92
- Unspecified	13

N: number of cases

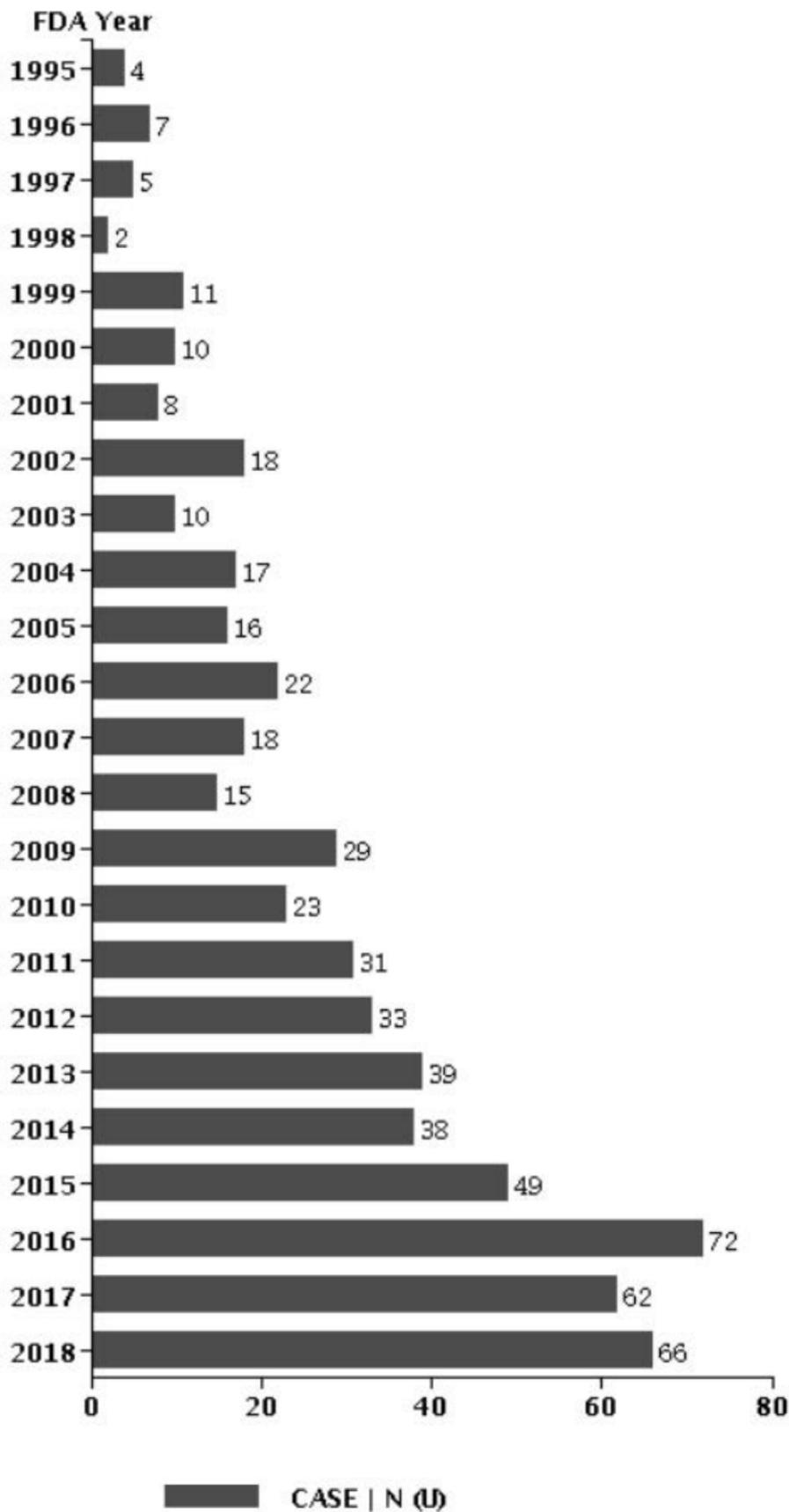**Table 2:** Association of Age with Tramadol Related Hypoglycemia

Age Group (years)	N	LROR	LR05	LR95
00-01	655	3.2007	3.0240	3.3776
02-04	383	2.9005	2.6853	3.1167
05-12	625	1.5709	1.4445	1.7041
13-16	442	1.3720	1.2357	1.5186
17-45	5784	1.1490	1.1060	1.1931
46-75	15774	1.1177	1.0816	1.1549
76-85	4807	1.4950	1.4279	1.5643
86-above	1362	1.6644	1.5466	1.7876

N: number of cases; LROR: logistic regression odd-ratios; LR05: fifth percentile of the logistic regression odd-ratios, LR05 ≥ 2 is considered significant; LR95: ninety-fifth percentile of the logistic regression odd-ratios

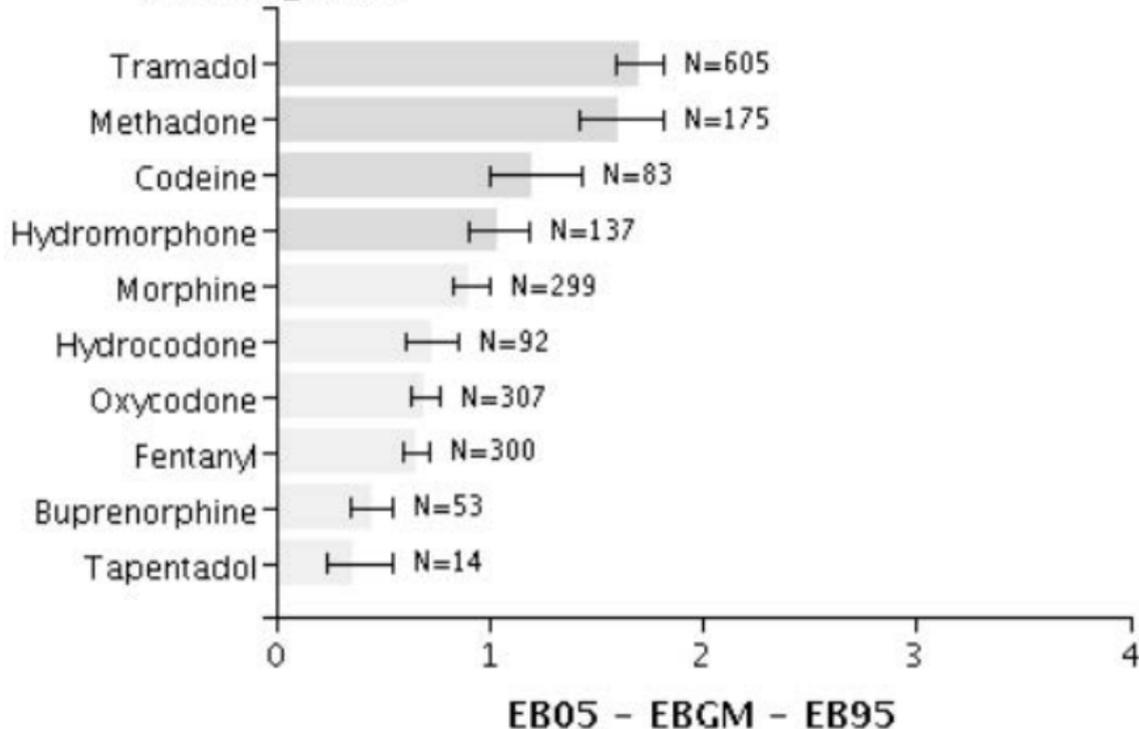**Figure 1:** Tramadol Related Hypoglycemia Cases by Year

Figure 2: Association of Opioids with Hypoglycemia

EB05: fifth percentile of the Empirical Bayesian geometric mean distribution, EB05 > 2 is considered significant; EBGM: Empirical Bayesian geometric mean; EB95: ninety-fifth percentile of the Empirical Bayesian geometric mean distribution

FDA Year	CASE | N (U)
1995	4
1996	7
1997	5
1998	2
1999	11
2000	10
2001	8
2002	18
2003	10
2004	17
2005	16
2006	22
2007	18
2008	15
2009	29
2010	23
2011	31
2012	33
2013	39
2014	38
2015	49
2016	72
2017	62
2018	66

Event=Hypoglycaemia

Generic_Name

Generic Name	EB05 – EBGM – EB95	N
Tramadol	⊢●⊣	N=605
Methadone	⊢●⊣	N=175
Codeine	⊢●⊣	N=83
Hydromorphone	⊢●⊣	N=137
Morphine	⊢●⊣	N=299
Hydrocodone	⊢●⊣	N=92
Oxycodone	⊢●⊣	N=307
Fentanyl	⊢●⊣	N=300
Buprenorphine	⊢●⊣	N=53
Tapentadol	⊢●⊣	N=14

EB05 – EBGM – EB95

$0 \leq EBGM \leq 1 < EBGM \leq 2 < EBGM \leq 4 < EBGM \leq 8 < EBGM < \infty$